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ORIGINAL ARTICLE

Clinical risk factors of prediabetes in Taiwanese women without substance uses (tobacco, alcohol, or areca nut)

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Background/Purpose: Individuals with prediabetes (100–125 mg/dL) and diabetes mellitus (DM) increase the risk of all-cause and cardiovascular disease (CVD) mortality. Since personal substance use such as cigarette smoking, alcohol drinking, and areca nut chewing may confound the true effect of clinical biochemistries on the risk of prediabetes, this study aims

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to examine the relationship between clinical biochemical parameters and the risk of prediabetes among Taiwanese without the habits of consuming tobacco, alcohol drinking, or areca nut.
Methods: Women aged between 40 years and 64 years who came to one community teaching hospital between January 1, 2001 and December 31, 2008 for general health screening for the first time were studied. The general health screening is provided every 3 years gratis. The package of this health screening includes personal history, physical examination, and biochemical tests in serum and urine.
Results: In total, 8580 nonsmoking, nondrinking, and nonareca nut chewing women who did not have a history of DM were eligible for this study. Of these, 1861 (21.7%) out of 8580 women were prediabetic. Compared to women with normal fasting glucose (NFG), we found a dose-response relationship of the risk of prediabetes with age and body mass index (BMI) and total cholesterol, triglyceride, glutamic-pyruvic transaminase (GPT), and uric acid in serum. Women with hypertension or proteinuria ($\geq$30 mg/dL) had also an increased risk to have prediabetes.
Conclusion: Besides age, the factors of BMI, hypertension, dyslipidemia, GPT, hyperuricemia, and proteinuria are the main risk factors for prediabetes in Taiwanese women without substance uses. A follow-up study is necessary to clarify the causality of these important biochemical parameters and prediabetes.

Introduction

Diabetes mellitus (DM) is well known to increase the risk of all-cause and cardiovascular disease (CVD) mortality.[1–3] The associated cardiovascular risk factors are connected with the development of micro- and macrovascular complications in the course of the disease,[4,5] and sometimes even prior to the diagnosis of diabetes. Recognition is now growing that even nondiabetic levels of hyperglycemia, as observed in impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), may also be associated with an elevated risk of CVD and premature mortality.[4,6,7] IFG, traditionally defined as 110—125 mg/dL, is an independent risk factor and should be aggressively treated as a disease, because it produces a significant increase in combined CVD and diabetes mortality risks in Asian populations.[8] Although the Diabetes Risk Calculator is a readily available, noninvasive screening tool to detect both prediabetes and undiagnosed diabetes in the US population,[9] few studies have identified the risk factors of prediabetes in healthy Taiwanese populations for subsequent intervention.

Substance use including cigarette smoking, alcohol drinking, and areca nut chewing have been reported to be associated with DM. Experimental studies have shown that cigarette smoking can impair insulin action mainly through decreasing peripheral glucose uptake and leading to an insulin-resistant state. Moreover, it is well known that smoking is associated with chronic inflammation, which is a predictor of the transition from normoglycemia to IFG and increases the risk of type 2 diabetes.[10,11] Although moderate alcohol drinking was associated with a reduced risk of type 2 diabetes, heavy alcohol drinking was associated with an increased risk of type 2 diabetes.[12–14] For areca nut chewing, it was linked to the newly diagnosed type 2 DM.[15,16] The prevalence of cigarette smoking, alcohol drinking, and areca nut chewing in Taiwanese women is relatively low.[17] By contrast, our previous study has found that the prevalence of use of any substance was more than half ($\sim$53%) in Taiwanese healthy men who were from community residences and attended the hospitals for routine physical checkups.[18] To avoid the significant influence of substance use on the relationship between clinical biochemical factors and prediabetes, we only focused on women who did not have any habit of substance use in this study. In addition, there are few studies examining the clinical risk factors of prediabetes in Taiwanese women, thus we pursued this inquiry by analyzing the dataset of health screening in one community teaching hospital.

Materials and methods

Study design

The study participants were women aged between 40 years and 64 years who had come to one community teaching hospital located in Kaohsiung City of Southern Taiwan for general health screening between January 1, 2001 and December 31, 2008 for the first time. The general health screening is provided by the Taiwan government to its citizens every 3 years for free. The package of this health screening includes a history of chronic diseases and personal lifetime habits, physical examinations such as body height, body weight, and blood pressure monitoring, and a morning venipuncture with fasting at least 8 hours and collection of urine specimens for biochemistry parameters.

Information about personal lifetime habits included smoking cigarettes, drinking alcohol, and chewing areca nut or not; body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Blood pressure was measured using a standardized mercury column sphygmomanometer and an appropriately sized cuff after the individual had rested for at least 5 minutes. Two measurements were taken and the average of the two measurements was recorded.[19]

Definition of prediabetes

According to the American Diabetes Association (ADA), prediabetes is defined as a fasting serum glucose test of 100–125 mg/dL or an oral glucose tolerance test of 140–199 mg/dL. In this study, we defined the prediabetes group as when the fasting glucose was between 100 mg/dL and 125 mg/dL and no history of diabetes diagnosis or antidiabetic treatment was found. Thus, women with normal fasting glucose (NFG) were those with a serum glucose <100 mg/dL and no history of diabetes or antidiabetic treatment. In order to examine the risk of prediabetes in women, we excluded women with NFG >125 mg/dL, a past history of DM, or treatment of antidiabetic agents.

Statistical analysis

Mean ± standard deviations or numbers with frequency were used to describe the demographic characteristics and clinical biochemistries when appropriate. Initially, multivariate logistic regression analyses were used to identify significant determinants of prediabetes after adjusting for age. When the significance of one covariate reached $p < 0.05$, that variable was further placed in the logistic regression models. Results derived from the logistic regression model were shown as odds ratio and 95% confidence interval (CI).

The continuous variables were categorized by quintile or based on the normal ranges in the clinical settings. These variables included BMI and total cholesterol, triglyceride, glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), uric acid, blood urea nitrogen (BUN), and creatinine in serum. For BMI, we classified individuals, based on the definition from the Bureau of Health Promotion of the Taiwan Government, as less-than-ideal weight (BMI $<$ 18.5), ideal weight (18.5 $\leq$ BMI $<$ 24), overweight (24 $\leq$ BMI $<$ 27), and obese (BMI $\geq$ 27). For biochemical parameters, the clinical abnormalities of serum GOT, GPT, BUN, creatinine, and uric acid were >33 IU/L, > 34 IU/L, >21.1 mg/dL, >1.5 mg/dL, and >8.3 mg/dL, respectively. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or participants with a history of hypertension or treatment with antihypertensive agents.

All statistical tests were two-tailed and $p < 0.05$ was considered as statistically significant. All data were analyzed by JMP (version 7.0) and SAS (version 9.1) software (SAS Insitute Inc., Cary, NC, USA).

Results

Between January 1, 2001 and December 31, 2008, 12,183 women received health screening in this community teaching hospital (Fig. 1). After excluding women with any history of substance uses (tobacco, alcohol, or areca nut, $n = 221$), known DM status ($n = 948$), unknown glucose status or no information of serum glucose ($n = 186$), and lack of any information about biochemistries (total cholesterol, triglyceride, GOT, GPT, BUN, creatinine, or uric acid in serum or protein or white blood cells in urine) or BMI ($n = 2248$), 8580 women were eligible and were included for subsequent analyses. Mean age (±standard deviation) in these 8580 eligible women was 49.9 (±6.6) years, similar to those individuals who lacked information about biochemistries or BMI (50.4 ± 6.7; $n = 2248$).

It was found that 1861 (21.7%) of 8580 women had fasting serum glucose testing between 100 mg/dL and 125 mg/dL. Compared to NFG women, we found higher BMI and total cholesterol, triglyceride, GOT, GPT, BUN, and uric acid in serum were more frequent in prediabetic women after adjusting for age (Table S1). Women with hypertension also increased the risk of prediabetes. In addition, women with proteinuria (≥30 mg/dL) had a higher risk of having prediabetes. After considering all significant variables in the model, we found a dose-response relationship between the risk of prediabetes and age and BMI and total cholesterol, triglyceride, GPT, and uric acid in serum (Table S1). By contrast, serum GOT levels were negatively and significantly associated with the risk of prediabetes. Women with hypertension or proteinuria (≥30 mg/dL) remained at risk of prediabetes in the full model.

When categorizing BMI and biochemistries based on the clinical references of normal ranges, we found the majority of the results were similar to those categorized by quintiles (Table 1). Similar results were found in the variables of age, BMI, hypertension, and proteinuria and total cholesterol, triglyceride, GPT, and uric acid in serum. For GOT, the negative and significant association with the risk of prediabetes was not present. By contrast, women with abnormal serum BUN levels (>21.1 mg/dL) had a 1.25-fold risk (95% CI = 1.01–1.55) to have prediabetes compared to women with normal BUN levels (Table 1).

Discussion

In our study, 21.7% of women had IFG. The prevalence rate in our study was higher than that in the community survey from the Bureau of Health Promotion in 2002 (5.2% in women).[20] The possible explanations are: firstly, the definition of IFG in our study was 100–125 mg/dL according to ADA, but the definition of IFG in that study was 110–125 mg/dL by the World Health Organization; secondly, the sources of participants in our study were not only from the community, but also patients from outpatient departments who might not be healthier than those from the community; and thirdly, although we encouraged the study participants to fast for at least 8 hours, this behavior could not be guaranteed. However, the potential bias could only introduce underestimation of our findings in this study.

There is evidence that factors are independently associated with the development of diabetes, such as age, family history of diabetes, waist-to-hip ratio, BMI, blood pressure, and lipid profile levels. Current evidence shows that the prevention of type 2 diabetes is possible through lifestyle intervention in high-risk individuals, such as prediabetics[20–22] in whom beneficial changes in dietary and exercise behaviors have been associated with reductions in several risk factors for CVD. Some diabetes risk scores based on simple, noninvasive, and inexpensive tools for high-risk groups of type 2 diabetes have been reported.[9,23,24] An important step in preventing or delaying

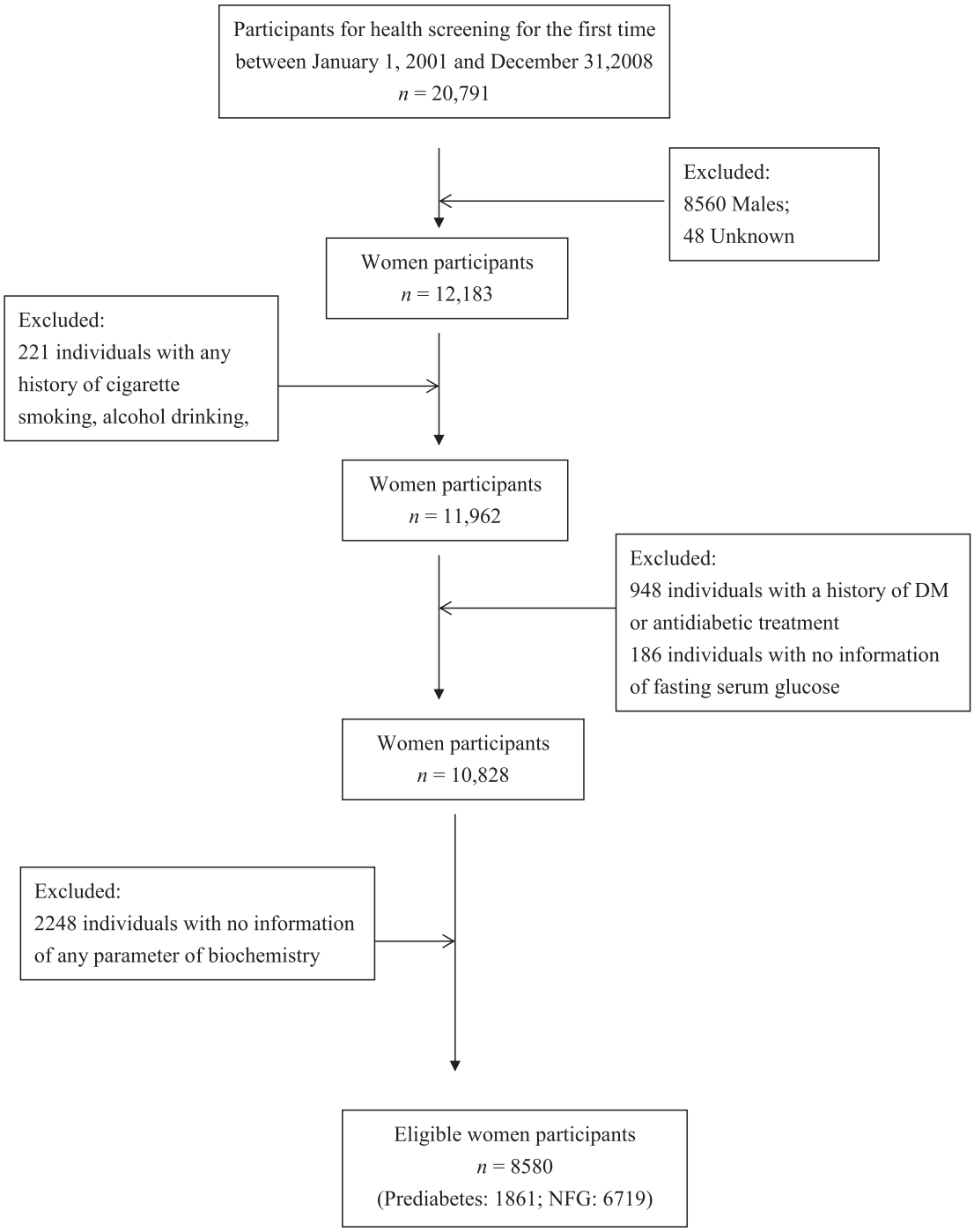

Figure 1 Study flowchart. DM = diabetes mellitus; NFG = normal fasting glucose.

type 2 diabetes and its complications is to identify people with prediabetes and undiagnosed diabetes so that they can be given appropriate care.

Several risk factors of prediabetes in our study are similar to those of DM, including metabolic syndrome (overweight, hyperlipidemia, and hypertension),[25] hyperuricemia,[26] and proteinuria.[27,28] In addition to those known clinical parameters, liver function impairment, particularly serum GPT, is one of the major risk factors for prediabetic women. We found that serum GPT levels within the normal range (<34 IU/L) were still a risk factor for prediabetes. GPT is a well-known specific marker of liver pathology and of nonalcoholic fatty liver disease. It may also be associated with obesity, fatty liver, or other hepatitis history. Alternatively, insulin resistance has been reported to be common in those with nonalcoholic fatty liver disease.[29,30] The pathogenesis of the association between high GPT among nondrinkers and light drinkers and the risk of type 2 DM might be in part due to nonalcoholic fatty liver disease and insulin resistance. One study has shown that

Table 1 Relationship of demographic characteristics and clinical biochemical factors categorized by clinical normal ranges with the risk of prediabetes in Taiwanese women.

	NFG N ()	Prediabetes	p[a]	AOR (95% CI)[b]	AOR (95% CI)[c]
	n (%)	*n* (%)			
Age (y)			<0.0001		
40–44	2041 (30.4)	338 (18.2)			1.00
45–49	1721 (25.6)	379 (20.4)			1.15 (0.98–1.36)
50–54	1574 (23.4)	537 (28.9)			1.53 (1.31–1.80)
55–59	844 (12.6)	332 (17.8)			1.57 (1.31–1.89)
60–64	539 (8.0)	275 (14.8)			1.93 (1.58–2.35)
BMI (kg/m^2)			<0.0001		
<18.5	189 (2.8)	19 (1.0)		0.54 (0.32–0.85)	0.61 (0.36–0.96)
18.5–23.9	3647 (54.3)	678 (36.4)		1.00	1.00
24.0–26.9	1775 (26.4)	593 (31.9)		1.67 (1.47–1.89)	1.42 (1.25–1.61)
>26.9	1108 (16.5)	571 (30.7)		2.50 (2.19–2.85)	1.87 (1.62–2.15)
Hypertension			<0.0001		
No	5434 (80.9)	1213 (65.2)		1.00	1.00
Yes	1285 (19.1)	648 (34.8)		1.87 (1.66–2.11)	1.52 (1.34–1.71)
Total cholesterol (mg/dL)			<0.0001		
<200	3002 (44.7)	633 (34.0)		1.00	1.00
200–239	2475 (36.8)	729 (39.2)		1.29 (1.15–1.46)	1.16 (1.02–1.31)
≥240	1242 (18.5)	499 (26.8)		1.61 (1.40–1.85)	1.31 (1.14–1.52)
Triglyceride (mg/dL)			<0.0001		
<150	5438 (80.9)	1268 (68.1)		1.00	1.00
150–199	718 (10.7)	297 (16.0)		1.63 (1.40–1.90)	1.26 (1.08–1.48)
200–499	545 (8.1)	273 (14.7)		1.92 (1.64–2.25)	1.33 (1.12–1.58)
≥500	18 (0.3)	23 (1.2)		5.01 (2.68–9.50)	3.17 (1.66–6.14)
GOT (IU/L)			<0.0001		
≤33	6323 (94.1)	1686 (90.6)		1.00	1.00
>33	396 (5.9)	175 (9.4)		1.46 (1.21–1.76)	0.89 (0.69–1.16)
GPT (IU/L)			<0.0001		
≤34	6062 (90.2)	1534 (82.4)		1.00	1.00
>34	657 (9.8)	327 (17.6)		1.82 (1.57–2.10)	1.51 (1.23–1.85)
BUN (mg/dL)			<0.0001		
≤21.1	6381 (95.0)	1700 (91.4)		1.00	1.00
>21.1	338 (5.0)	161 (8.7)		1.42 (1.16–1.73)	1.25 (1.01–1.55)
Creatinine (mg/dL)			0.041		
≤1.5	6650 (96.8)	1825 (98.1)		1.00	1.00
>1.5	69 (1.0)	36 (1.9)		1.56 (1.03–2.35)	0.87 (0.55–1.36)
Uric acid (mg/dL)			<0.0001		
≤8.3	5376 (80.0)	1211 (65.1)		1.00	1.00
>8.3	1343 (20.0)	650 (34.9)		1.90 (1.70–2.14)	1.38 (1.22–1.56)
Proteinuria (mg/dL)			<0.0001		
0 or < 30	6506 (96.8)	1736 (93.3)		1.00	1.00
≥30	213 (3.2)	125 (6.7)		2.05 (1.63–2.58)	1.52 (1.18–1.95)
WBC in urine/HPF			0.079		
0	4288 (63.8)	1,135 (61.0)		1.00	
1–5	1922 (28.6)	571 (30.7)		1.11 (0.99–1.24)	
>5	509 (7.6)	155 (8.3)		1.14 (0.94–1.39)	

BMI = body mass index; CI = confidence interval; HPF = high power field; NFG = normal fasting glucose; WBC = white blood cell; GOT = glutamic-oxaloacetic transminase; GPT = glutamic-pyruvic transaminase; BUN = blood urea nitrogen.

[a] Crude analyses.

[b] Adjusting for age.

[c] Model includes variables of age, body mass index (BMI), hypertension, total cholesterol, triglyceride, glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), blood urea nitrogen (BUN), and uric acid in serum and proteinuria.

nondrinkers with the highest GGT or GPT had a high risk of type 2 diabetes.[31] Our study further showed that GPT is associated with prediabetes among nonsmoking and nondrinking women.

Several limitations were present in this study. Information about the lifetime consumption of tobacco, alcohol, and areca nut were collected from the questionnaire. Thus, their accuracy is doubtful. To solve this problem, we can

measure several established exposure biomarkers in different human specimens such as urinary cotinine for cigarette smoking, serum acetaldehyde for alcohol drinking, and tissue safrole-DNA adduct for areca nut, which have proved the accuracy of questionnaires in one of our previous studies.[32] However, that strategy can only partly solve the issue of current exposure, rather than long-time exposure. Thus, it needs to combine a prospective cohort design with regular follow-up to routinely collect the information about those substance uses to solve the limitation of recall bias. Alternatively, to search the novel biomarkers representative for a long-term exposure of substance uses is necessary. In addition, information about family history of DM is lacking in this study. Thus, we were unable to evaluate the impact of family history of DM on the relationship between clinical risk factors and prediabetes. Because this study only focused on women, and lifestyle habits, genetic expressions, and disease entity are different between men and women, our findings cannot be generalized to the male population. Surprisingly, we found that women who were underweight (BMI $<$ 18.5), compared to those with normal weight (BMI $=$ 18.5–23.9), had a significantly lower risk of having prediabetes. Our explanation is that underweight women are likely to co-exist with DM[33] which those women were excluded from this study due to cross-sectional design and cause the status of underweight to be less likely to be prediabetes. It is necessary to elucidate the real mechanism of this phenomenon in the future. Finally, this is a cross-sectional study; thus, the issue of causality cannot be addressed.

By contrast, the strength of this study is to focus on the effect of the clinical biochemical parameters on the risk of prediabetes among women who did not have any history of substance use. Our findings will be useful for general practitioners or family physicians to identify the high-risk group of DM in women in the clinical setting.

In conclusion, in addition to age, BMI, hypertension, dyslipidemia, GPT, hyperuricemia, and proteinuria are the main risk factors of prediabetes in Taiwanese women. A follow-up study is necessary to clarify the causality of these important biochemical parameters and prediabetes in women.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jfma.2014.10.007.

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